Mycopathologia (2014) 178:291–295
DOI 10.1007/s11046-014-9805-x

Primary Cutaneous Mucormycosis in a Patient with Burn Wounds Due to *Lichtheimia ramosa*

Ravinder Kaur · Kiran Bala · Rajeev B. Ahuja · Prabhat Srivastav · Umesh Bansal

Received: 13 May 2014 / Accepted: 20 August 2014 / Published online: 29 August 2014

Abstract Mucormycosis is usually an invasive mycotic disease caused by fungi in the class mucormycetes. Here we report a case of cutaneous mucormycosis due to *Lichtheimia ramosa* in a 20-year-old female patient with burn injuries. She was admitted to the hospital with accidental flame burns covering 60 % total burn surface area. After 15 days of admission to hospital, the burn wound showed features of fungal infection. Culture showed white cottony growth belonging to the Mucorales order. Morphological identification confirmed it as *L. ramosa*. She was managed surgically and medically with the help of amphotericin B. Patient survived due to prompt diagnosis and appropriate medical and surgical treatment. Early diagnosis is critical in prevention of morbidity and mortality associated with the disease. Fungal infection in burn wounds can be difficult to diagnose and manage.

Keywords *Lichtheimia ramosa* · Mucormycosis · Burn · Amphotericin B

R. Kaur (✉) · K. Bala
Department of Microbiology, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi 110002, India
e-mail: drkaur@hotmail.com; drkiran.dks@gmail.com

R. B. Ahuja · P. Srivastav · U. Bansal
Department of Burn and Plastic Surgery, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi, India

Introduction

Fungal infections in patients with burns greater than 50 % total body surface area are seen to be associated with significant morbidity and mortality [1, 2]. This group of patients have a greater susceptibility due to altered immune function and lost skin protection [1]. Mucormycosis is an invasive fungal infection caused by order Mucorales. The genera reported to cause invasive infection are *Absidia*, *Mucor, Rhizomucor, Rhizopus, Apophysomyces, Saksenaea, Cunninghamella, Cokeromyces* and *Syncephalastrum*. *Rhizopus* is the most common genus causing human Mucormycetes infections in most case series, followed by genera such as Mucor and Lichtheimia, accounting for 70 to 80 % of all mucormycosis cases. These fungi are ubiquitous in environment; they can cause a rapidly progressive and fatal disease in compromised hosts. The genus *Lichtheimia* (syn. *Mycocladus*, *Absidia proparte*) belongs to the order Mucorales and includes saprotrophs isolated from soil, decaying plant material or dung [1, 2]. Three out of five currently accepted species, namely *Lichtheimia corymbifera*, *Lodderena ornata* and *Lichtheimia ramosa*, are known to cause human infections (mucormycoses) predominantly in patients with impaired immune systems [2]. The awareness about the thermotolerant genus *Lichtheimia* has increased markedly since its separation from the mesophilic genus *Absidia* and its taxonomic revision and has also been seen to result in a significantly higher number of reports of infections assigned to

Lichtheimia [2, 3]. In the recent past, the proportion of mucormycosis by *Lichtheimia* species as reported in comprehensive studies has risen from 5 to 29 % [4–7]. The spectrum of diseases includes a variety of rhinocerebral, pulmonary, gastrointestinal, cutaneous and disseminated infections. Patients with a disruption of the normal protective cutaneous barrier are at maximal risk of developing cutaneous mucormycosis. Local risk factors for cutaneous mucormycosis include trauma, burns, surgery, surgical splints, arterial lines, injection sites, biopsy sites, tattoos, and insect or spider bites [8, 9]. Systemic risk factors for cutaneous mucormycosis have been seen to be hyperglycaemia, ketoacidosis, malignancy, leucopoenia and immunosuppressive therapy [10, 11]. The majority of cases caused by *Lichtheimia* species relate to patients who are severely debilitated due to malignancies, poorly controlled diabetes or solid organ transplantation [12]. Cutaneous, pulmonary, rhinal, rhinocerebral, renal, [12–16] and disseminated infections [17, 18] as well as gastrointestinal [19] and otomycosis [20] have been described and hence a widespread spectrum of infections due to *Lichtheimia* spp. similar to that of other members of the Mucorales. The outcome of cutaneous mucormycosis is seen to depend on the progress of the underlying disease along with the early diagnosis and treatment initiated.

In the present case report, we describe post-burn primary cutaneous mucormycosis due to *L. ramosa.*

Case Report

A 20-year-old female was admitted in emergency with deep dermal to full thickness 60 % TBSA burn in the Department of Burn and Plastic Surgery, Lok Nayak Hospital. She had sustained accidental flame burns while cooking. She was successfully resuscitated with ringer lactate and plasma expander. The wounds were managed by sequential debridement and daily dressings with topical antimicrobials with all aseptic and antiseptic precautions. Broad spectrum antibiotics were given IV as per wound swab culture sensitivity report. The vitals remained stable for 10 days. However, she developed fever, tachycardia, tachypnoea on day 14. The wounds over both thighs which were initially deep dermal, converted to full thickness injury. Liquefaction and necrosis was observed which led to rapid separation of eschar from upper thighs.

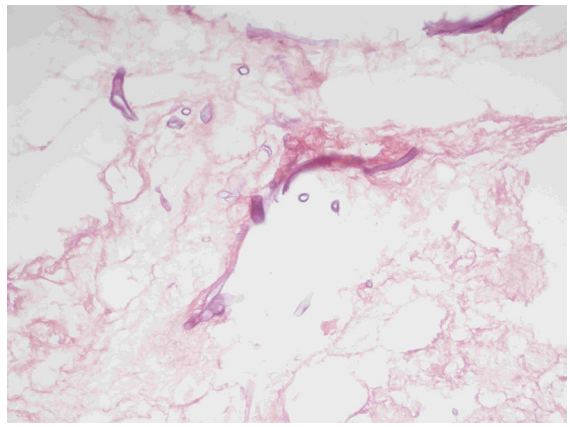

Fig. 1 Periodic acid schiff staining (PAS) from biopsied material revealed a granulomatous and suppurative inflammatory lesion with irregular, long, aseptate fungal hyphae with right angle branching

The lesion was surgically debrided, and biopsy samples were sent for HPE and microbiological processing (Fig. 1).

Laboratory investigations revealed: Haemoglobin 9 g/dl, white blood cell count 18 $\times$ 10^3, platelets 6 lakh/cumm, serum creatinine 0.4 mg/dl, blood urea 21 mg/dl, random blood sugar 83 mg/dl. The patient was administered broad spectrum antifungal amphotericin B in dose of 3 mg/kg per day for 3 weeks along with broad spectrum antibiotics (inj. Imipenem 500 mg IV 8 h $\times$ 7 days). Daily dressings were continued, and nutritional support was maintained with IV supplements. The lesion was debrided, and biopsy sample was sent for microbiological and histopathological examination. The bacterial culture of wound swab showed the growth of *Escherchia coli* and *Pseudomonas aeruginosa*, both were sensitive to polymyxin B and colistin and Netilmicin. The KOH wet mount and histopathological examination of biopsy specimen showed aseptate, broad, ribbon-shaped hyphae with right angle branching suggestive of mucormycosis. The biopsy material was cut into small pieces and inoculated onto 2 sets of Sabouraud dextrose agar supplemented with chloramphenicol and gentamicin and without antibiotics. One set of tubes was incubated at 22 °C and other one at 37 °C. After 24 h of incubation, a white floccose growth was obtained in both the tubes which turned grey on further incubation within 2–3 days (Fig. 2). The lactophenol cotton blue mounts were made and examination revealed broad, aseptate branching hyphae. Rhizoids

Fig. 2 White cottony growth of *L. ramosa*

Fig. 3 Lactophenol cotton *blue* preparation showing pear-shaped sporangia and prominent conical columella

were not observed. The sporangia were pear shaped and had prominent conical columella. No corymb formation was seen in this fungus. Microscopic examination of this strain showing branched sporangiophores with characteristic circinate side branches and pleomorphic giant cells with finger-like projections. A funnel-shaped apophysis was evident beneath the sporangium consistent with fungi of the order Mucorales. All phenotypic characteristics confirmed it as *L. ramosa*. A repeat biopsy was taken after 6 days, and it also showed broad, aseptate hyphae in KOH wet mount and culture on SDA also revealed a similar growth which after LCB examination confirmed *L. ramosa* (Fig. 3).

Surgical debridement and aseptic dressing of wound under antibiotic coverage was done daily. Conventional amphotericin B 3 mg/kg was started along with serum urea and creatinine levels monitoring. The affected wound showed improvement with decrease in necrotic sloughness and firm healthy granulation tissue was developing. Patient's condition had improved, was discharged after 15 days and followed up regularly. Early suspicion and diagnosis with prompt management helped to save the patient.

Discussion

Recently, the genus *Absidia* has been revised based on physiological, morphological and molecular phylogenetic data, and the name *L. corymbifera* has been proposed for *Absidia corymbifera* [2]. *Lichtheimia* genus comes under the family Lichtheimiaceae [21].

The first case of *L. corymbifera* infection was reported by Hiller in 1874 [22]. Invasive infections with this fungus usually occur in individuals and carry a grave prognosis [23–26]. It is known to be responsible for approximate 5 % of culture confirmed cases of mucormycetes infections [27]. The organism is ubiquitous in nature, and the infection occurs as a result of inhalation of spores or the direct inoculation of spores into the tissue [28]. Infections with this organism encompass the entire spectrum of mucormycetes disease manifestation including cutaneous and subcutaneous, rhinocerebral, pulmonary, gastrointestinal and disseminated disease [29–31]. The clinical manifestation of cutaneous mucormycosis ranges from non-healing ulcers to rapidly proliferating necrotising fasciitis [31]. Cutaneous infections with *L. corymbifera* manifest as grey black plaques that rapidly increase in size over a 12- to 24-h period. Lopes et al. described an unusual case in which the infection probably resulted from latent osteomyelitis. Various infections involving external ear, skin, subcutaneous tissue and even bone necrosis in a malnourished child; a granulomatous ulcer of the foot, facial cellulitis and lymphomatoid papulosis have been reported. Primary cutaneous mucormycosis has also been reported in a patient with AIDS and in two patients who had undergone bone marrow transplantation. There has been also a case report of pulmonary mucormycosis due to *L. ramosa* in an AIDS patient [32]. About 40 % of patients sustaining cutaneous mucormycosis are found to be immunocompetent [3].

A significant number of reported *A. corymbifera* (*L. corymbifera*) infections are *L. ramosa* infections which are of global distribution. The study done by Woo et al. [33], they collected and re-characterized the 13 published strains of *A. corymbifera* (*L. corymbifera*) from Spain, France and Qatar, and all were unambiguously identified as *L. ramosa* using both phenotypic and genotypic methods. These 13 strains were obtained from diverse sites, including the respiratory tract, paranasal sinuses, brain, heart, blood and wound, implying that *L. ramosa* could be the cause of different clinical forms of mucormycosis. They had also been reported the three cases of *L. ramosa* as: the first a causative agent in liver transplant recipient with rhinocerebral mucormycosis, the second a renal transplant recipient with gastrointestinal mucormycosis and the third a burn patient with cutaneous mucormycosis [34].

Trauma is the most important predisposing factor for this infection in patients with normal immune functions. In contrast, disseminated infections are more often restricted to immunocompromised hosts [30]. Bibashi et al. [35] described a mycosis due to *L. ramosa* in a young male patient with multiple traumatic fractures due to accident that was also healed by surgical debridement with cleansing with antimycotic solution, without the need for systemic antimycotics. There have been case reports of cutaneous mucormycosis due to *L. ramosa* in a diabetic patient with severe occlusive arterial disease [36]. There have been cases of nosocomial cutaneous mucormycosis where the pathogen entered the human body via surgical wound sites or insertion sites of intravenous catheters [29]. There have been reports on nosocomial cutaneous mucormycosis due to *Lichtheimia* spp. (ex *Absidia/Mycocladus*) in the intensive care and orthopaedic units due to cross-transmission [37]. Infections of immunocompetent hosts have occasionally been reported from all important pathogenic mucoralean species including *Lichtheimia* [31, 32]. Necrotising fasciitis caused by *Apophysomyces elegans* or *Rhizopus arrhizus* has also been observed in immunocompetent hosts. The fungal spores germinate and the fast growing mycelium invades blood vessels, leading to a reduced blood supply and vitality of the tissue, followed by necrosis and possibly also due to decreased levels of antifungals in the tissue. Intensive debridement should be included in the treatment of this infection for cure [29–32]. Treatment of cutaneous mucormycosis involves combination of surgical debridement and appropriate antifungal therapy. *L. ramosa* are seen to exhibit low MICs for AmB (0.25–0.5) and posaconazole (0.06–0.25). Treatment with amphotericin B and posaconazole helps in survival of the patients.

In most cases, cutaneous mucormycosis is difficult to manage. Clinical diagnosis is difficult with various patterns of disease ranging from indolent ulceration (on the diabetic or immunocompromised limb), to the rapidly progressive necrosis associated with patients with major trauma. Wound swabs are often negative, and the pathological features of these fungi (angioinvasion) require the tissue specimens to be sought early and analysed at an appropriate facility.

Fungal infection in burn wounds can be difficult to diagnose and manage. A high index of clinical suspicion and early biopsy of affected area leading to a timely diagnosis is must for management of the patient in reducing the morbidity. The standard treatment is a combination of amphotericin B therapy, surgical debridement and reversal of underlying disease. Adjunctive therapy with hyperbaric oxygen therapy and granulocyte colony-stimulating factor should be considered along with the management of underlying immunosuppression (e.g., diabetes).

Acknowledgments We acknowledge the staff of Mycology unit of Microbiology Department of Maulana Azad Medical College and Burn and Plastic Surgery Department of Lok Nayak Hospital, New Delhi.

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